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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/813,781
Filing Date: March 07, 1997
Appellent(s): WEIDANZ ET AL.

Robert Buchanan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/5/2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying that there are no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellants statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief contains a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5759817	Barbas	6-1998

Chung et al., Proc. Natl. Acad. Sci. USA, vol 91, (December 1994), pp. 12654-12658.

Onda et al., Molecular Immunology, vol 32, no. 17/18, (1995) pp 1387-1397.

Huse et al., Journal of Immunology, vol 149, no. 12, (December 15, 1992), pp. 3914-3920.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 stand rejected under 35 U.S.C. 103(a) as unpatentable over Chung et al. in view of Barbas US 5,759,817, Onda et al., and Huse et al. for the reasons elaborated in the previous Office Actions. Appellants arguments have been considered and deemed not persuasive.

Chung et al. teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). Chung et al. further teaches one embodiment of human single chain TcR in which C-terminus of Vα domain is linked to N-terminus of Vβ chain via a 15 amino acid residue flexible amino acid linker and the C-terminus of the Vβ chain is linked to the beta chain constant domain (see Figure 1). In one embodiment the C terminus of Vβ chain is linked to an alkaline phosphatase (PI) protein tag (see page 12655). Chung et also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. Chung et al. teach that the TcR fusion protein can bind antigenic protein, thus teaching that the TcR fusion protein comprises an antigen binding pocket. Chung et al. teaches a TcR fusion protein comprising Vα-peptide linker-Vβ-C β linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see results section). Chung et al. disclose that the soluble form of TcR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) (see page 12656). Chung et al. teaches expression of said TcR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag. Chung et al. also disclose a scTcR in which comprises Vα-peptide linker-Vβ-C β GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) (see page 12655). Chung et al. further teach that TcR fusion proteins which do not contain the Cβ do not fold into the native conformation. The

scTcR disclosed by Chung et al. meet the length limitations of the Vα and Vβ region recited in claims 69 and 71. Chung et al. teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ fragment-protein tag (eg. GPI). Chung et al. does not teach a TcR fusion protein further comprising bacteriophage VIII coat protein. However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see column 2, third paragraph, single chain antibody). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28). Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular). One embodiment of the invention is disclosed to be

a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a construct of a single-chain of the T cell receptor by a peptide linker sequence wherein the single TcR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TcR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TcR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular). Huse et al. teach that fusion proteins comprising a fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TcR fusion protein comprising the Vα-peptide linker-Vβ -Cβ fragment-protein taught by Chung et al. linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TcR-

bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TcR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from human TcR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TcR component of the protein.

(11) Response to Argument

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 stand rejected under 35 U.S.C. 103(a) as unpatentable over Chung et al. in view of Barbas US 5,759,817, Onda et al., and Huse et al. for the reasons elaborated in the previous Office Action. Appellants arguments have been considered and deemed not persuasive.

Regarding appellants comments, while heterodimeric molecules are a preferred embodiment disclosed in Barbas , Barbas discloses:

"In another embodiment, the present invention contemplates a polypeptide comprising an insert domain flanked by an amini-terminal secretion signal domain and a carboxy-terminal filamentous phage coat protein membrane anchor domain." (column 14, first complete paragraph). Barbas et al. further disclose than said construct could include a

"receptor protein" (column 14, second paragraph), indicating that the disclosed method could be used for receptors per se (eg. single chain or heterodimeric or single chain heteromers). In addition, fully functional recombinant single chain T cell receptors (containing a Vα and Vβ) had already been produced by Chung et al. Furthermore, Chung et al. teach that **it would be desirable to produce single chain TcR using phage display techniques that had already been used to produce single chain antibodies** (see page 12658, first column, first paragraph of discussion section). Thus, Chung et al. disclose the desirability of producing single chain TcR using phage display techniques and an expectation that such constructs could be made using techniques already used to produce single chain antibodies. Regarding motivation to create the claimed invention, as per above, Chung et al. teach that it would be desirable to produce single chain TcR using phage display techniques that had already been used to produce single chain antibodies (see page 12658, first column, first paragraph of discussion section).

Regarding appellants comments about the single chain heteromeric TcR taught by Chung et al., Chung et al. teach that the GPI anchor is cleaved and the soluble TcR still has all the antigen binding properties of the TcR (see pages 12656-12658). Thus, the GPI anchor is not required for the soluble TcR to function, it is just used in one particular method of making the soluble TcR. Regarding motivation to create the claimed invention, Chung et al. discloses that it would be desirable to produce their TcR in a phage display system (see page 12658, first column). In addition, Barbas et al. teach

the advantages of their system for the production of peptides. Regarding reasonable expectation of success, both Barbas and Chung et al. **disclose use of phage display systems to produce single chain antibodies** (see column 2, fourth paragraph from bottom and page 12658, first column). Single chain antibodies have a Vh and Vl chain linked by a linker wherein the claimed invention has a TcR alpha and beta chain linked by a linker. In addition, the soluble single chain TcR molecules functions with or without the GPI linker indicating that the construct itself is functional. Additionally, the cited prior art discloses that a variety of different types of molecules had been produced using phage display technology. The MPEP section 2143.02 discloses:

OBVIOUSNESS REQUIRES ONLY A REASONABLE EXPECTATION OF SUCCESS

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)

Regarding appellants comments about Holler et al., said publication was published in **May 2000**. In the amendment filed 6/3/2000, applicant submitted a publication by Weidanz et al. (J. Imm. Methods **1998**) **which discloses the claimed invention**. Thus, it appears that ***Holler et al. simply are not familiar with the prior art or they are ignoring the prior art for the purposes of promoting their particular system.***

Thus, the comments of Holler et al. carry no weight **because two years prior to the Holler et al. publication, Weidanz et al. had already published data regarding the production of single chain TCR using bacteriophage**. Furthermore, Holler et al. discloses a yeast system for producing a single chain TCR and it appears that the main focus of Holler et al. is to promote their system.

successful.). In addition, the MPEP section 2143.02 discloses:

PREDICTABILITY IS DETERMINED AT THE TIME THE INVENTION WAS MADE

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986)

Regarding appellants comments about Huse et al., said reference discloses that: "The M131X31 and M131x12 vector system described here can serve as a versatile, general purpose approach to F(ab) production and screening." (See page 3919, second column). Thus, Huse et al. teach the general applicability of their system for producing f(ab) using phage display technology.

Regarding appellants comments about Onda et al., the entire purpose of the Onda et al. was to produce TcR **alpha chain** constructs to determine if the TcR **alpha chain** could bind antigen in the absence of TcR beta chain. Onda et al. found that some TcR alpha chains could bind antigen while others could not and that **this was the result of**

the inherently affinity of the particular alpha chain to bind antigen, not a failure in the process of making the construct (see abstract). Onda et al. conclude that TcR alpha which bind antigen in the absence of TcR beta chain do so because of the high binding affinity of the native TcR alpha chain for antigen (see page 1395, first column). The TcR alpha chain constructs disclosed by Onda et al. which do not bind antigen do not bind antigen because they require a TcR beta chain, not because of any problem with producing the TcR construct (see discussion). Onda et al. conclude that some TcR require alpha and beta chain to bind antigen whilst some TcR bind antigen mainly through the TcR alpha chain (see page 1395, second column).

Regarding applicants comments about Onda et al ., the instant rejection indicates that Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain of a T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). The art recognizes that the alpha and beta chains of the TCR generally both are involved in antigen binding. The art also recognizes that soluble TCR which bind antigen would have a variety of uses.

In conclusion, the instant rejection discloses why it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention (because the single chain TcR recited in the claims was known in the art as was use of phage display technology to produce a variety of different receptor molecules including single chain molecules such as single chain

antibodies). The instant rejection provides motivation to create the claimed invention (Chung et al. teach that **it would be desirable to produce single chain TcR using phage display techniques that had already been used to produce single chain antibodies** (see page 12658, first column, first paragraph of discussion section). The instant rejection provides a reasonable expectation of success because the TcR single chain molecule recited in the claim had already been produced using a different recombinant system, whilst a variety of different molecules (including single chain heteromeric receptor constructs such as single chain antibodies) had already been produced using phage display technology.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Ron Schwadron, Ph.D.

Primary Examiner

Art Unit 1644

January 24, 2005

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